Editorials

Plus Ça Change, Plus C'est la Même Chose

READERS MAY NOTICE DIFFERENCES in the journal with the arrival of the new editor. New color, typeface, subject headings (called "ears," strangely enough) reflect certain preferences. A broadening international presence, more opportunities for young authors, poetry and art, rigorous biostatistical and epidemiologic review all signal particular interests of the editor, the Editorial Board, and, of course, the readership.

Examination of our history, philosophy, and situation leads to the following reflections, which will inevitably affect the journal as it evolves and continues its mission to serve our profession.

- Change is part of life. As opportunities, requests, and circumstances change, the journal will adjust, too, just as it has in the past. We will thrive on change, not just survive it.
- The journal is strong, sound, and forward-looking. These attributes stem from the editorial leadership of decades: Dwight Wilbur, MD (1946-1967); Malcolm S. M. Watts, MD (1968-1990), Lloyd H. Smith, Jr, MD (1968-present); and the dedication of a small but skilled professional staff. The journal relies on the support of nine western medical associations, including, most recently, the Denver Medical Society. It also relies upon the endorsement and counsel of the physicians it serves. The journal's future will depend upon the continuation of that kind of leadership, dedication, and support—as well as searches for new approaches, audiences, and backing. The journal will continue its tradition of service as it focuses on the science, public policy, public health, ethics, and humanitarian issues that affect clinical medicine. We will continue to make a difference in physicians' and patients' lives.
- Physicians are citizens, mainly good ones, with hopes and dreams, families, preferences, frustrations, satisfactions, and, for the most part, a mission to serve others.
- Excellence is necessary and achievable in research, patient care, and publication. Highest quality peer review is essential to excellence.
- Medicine is difficult. The life is hard. We need to replenish our energy and soothe our souls. We need to go beyond the bounds, the bonds of our profession to do this.
- Medicine's science and art require constant learning. To be absorbed best, science writing must be honest, accurate, fair, and clear. It is usually best when it is brief, challenging, and has a certain panache.
- History, literature, performing arts, fine arts are important to medicine because they are important to patients and to physicians. In their own way, they are as important as technology and technique. It is interesting to explore the relationships between basic and applied sciences and the humanities. DNA is poetry.
- Physicians are part of society, and, fortunately, cannot escape it. We have talents that society needs beyond patient care. We must not allow ourselves to regard offices and hospitals as refuges. When we learn of the excess mortality in Harlem or the effects of toxic wastes, we cannot keep on with practice as usual, prescribing, patching, comforting. We must participate in the solution, not only the treatment. We must work particularly hard to prevent injury and illness if we cannot fix their awful aftermath—such as first trimester rubella and nuclear war.
- As society looks abroad for ideas and information, so will we. We are part of the Pacific Rim and will increasingly exchange science and medicine with that community.
- Although individuals accomplish great things, so do groups: the householders in Le Chambon who saved Jews in Occupied France; the framers of our Constitution; the synagogues and churches that establish retirement communities and AIDS programs. I most enjoy working in concert, not solo. I admire and value the volunteers who accomplish so many tasks, including the hundreds who volunteer to write and to review papers for the journal.
- Given excellence, diversity is good. Fostering diversity is necessary. In the journal, this means covering a wide range of topics—molecular genetics to ethics to occupational medicine—and publishing authors from different locales, perspectivies, and stages in training.
- Medicine is under fire, but there is no less need for kindness and compassion, and we must strive for a constructive, rather than defensive, response. You can help to keep us informed. Send ideas and observations; send bad news . . . and good.
- Physicians rarely have enough time to do necessary work, much less to reflect upon times gone by or the significance of events or to make wise plans. We will continue the tradition of making certain your time with THE WESTERN JOURNAL OF MEDICINE is well spent.

LINDA HAWES CLEVER

Growing Interest in Selenium

OVER THE PAST TWO DECADES, a dramatic expansion of interest has occurred in the biomedical community concerning the trace element selenium. Although selenium was found in the 1950s to replace vitamin E in the diets of experimental animals, both the metabolic bases for its nutritional functions and its relevance in human health remained unclear until the 1970s. The first breakthrough to understanding its nutritional role came when the element was found to be an essential component of glutathione peroxidase,[1] an enzyme that metabolizes peroxides including lipid hydroperoxides. This discovery revealed that selenium is involved, in concert with vitamin E, in protecting polyunsaturated membrane lipids from oxidative degradation that would result in membrane dysfunction. The second breakthrough came when the results of studies by Chinese scientists were made known to the rest of the world, showing for the first time that a clinical disorder, Keshan disease, was associated with selenium deprivation in humans.[2] That disease, which involves a multifocal myocarditis and, frequently, periacinar pancreatic fibrosis, affects mainly children and young women in a wide region of endemic selenium deficiency in China.[3(pp347-367)] While studies have shown that Keshan disease can be prevented by prophylactic treatment with selenium, its cause remains to be fully elucidated; nevertheless, it is clear that its endemic distribution is owed to severe selenium deficiency.

With these breakthroughs came a new appreciation for this element, which had hitherto been thought of only as a factor that spared the need for vitamin E and had special importance only in veterinary applications. Consequently, research activity involving selenium increased geometrically in the 1970s and 1980s. Epidemiologic investigations indicated inverse associations of tissue selenium concentrations and risks to cancer and heart disease. Studies using

animal tumor models showed that, when administered at supranutritional levels, several selenium compounds could delay or inhibit tumorigenesis. Clinical investigations revealed very low blood selenium concentrations—approaching those of patients with Keshan disease—in patients maintained for long terms by parenteral feeding or with other highly purified nutrient solutions of low selenium content. Studies of the nutritional biochemistry of selenium have demonstrated several selenium-containing proteins—in addition to the selenium-dependent glutathione peroxidase—in animal tissues, suggesting that the element may have other as-yet-unrecognized metabolic functions.[4] Recent studies of the molecular biology of selenium have found the element to be incorporated specifically into selenocysteinyl residues of selenium-dependent glutathione peroxidase and other selenoproteins through a novel cotranslational process involving the codon UGA, which was previously thought only to signal the termination of messenger RNA synthesis.[4] Studies in China showed the quantitative relationship of selenium-dependent glutathione peroxidase activity and selenium intake in human volunteers. Gradually the body of knowledge accumulated to the point where estimates of human selenium requirements became possible.[3(pp386-388),5]

It should be noted that this expansion of interest and information came against a background of healthy skepticism on the part of many scientists and clinicians. After all, long before selenium was ever considered to be a nutrient, it had been well known for its toxic potential. In fact, the first recognition that selenium had any biologic activity came in the 1930s when it was found to be the principle toxin associated with neuropathies and dermatopathologies of grazing horses and cattle in the northern Great Plains.[6] Perhaps it is this background, as well as the continuing lack of information concerning either the metabolic basis of selenium toxicity or the quantitative toxicities of various selenium compounds, that has caused some groups to be extremely conservative in their estimations of the window of safe exposure to this element.[7(p178)]

The issue of the safe range of selenium intake is a most important one today for reasons concerning the use of selenium supplements. For example, it is now apparent that selenium supplementation is highly appropriate for total parenteral nutrition solutions and, perhaps, some low-selenium infant formulas. In addition, the voluntary use of over-the-counter selenium supplements is growing, apparently because of putative health benefits of the nutrient. Should any of the intervention studies now in progress find selenium supplementation to reduce cancer risk or to have some other health benefit, the use of over-the-counter selenium supplements can be expected to increase further. Addressing issues of the safety or toxicity of selenium involves both quantitative and qualitative considerations. One must be able to answer the compound question, "What doses of what compounds of selenium are safe?" Unfortunately, data relevant to these considerations are limited, but speculation is not.

In this issue, Fan and Kizer have reviewed information from the biomedical literature to provide background on selenium and health for those with limited direct experience in this area.[8] Their review addresses both the nutritional and toxicologic significances of selenium, with greater emphasis on the latter. This is, perhaps, not surprising for, as they acknowledge, one of the factors to have stimulated recent interest in selenium, particularly in California, is the occurrence of selenosis among waterfowl in the San Joaquin Valley drainage.[9] In fact, they present an excellent discussion of selenium intoxication effected by various means.

An anchoring concept important to that review is that any consideration of the biologic activities of selenium necessarily entails considerations of several different chemical compounds of the element. Thus, the authors' statements to the effect that "selenium can be a toxicant" must not be misread. In understanding the role of selenium in nutrition and health, it is important to keep in mind the differential metabolic use that is known to occur for the several chemical forms of selenium to which people may have exposure. All compounds of selenium are not alike in terms either of solubility, distribution in the environment, metabolism, nutritional value, or toxicity.

Another point that should be emphasized concerns the irregular geographic distribution of selenium in soils and, hence, in food chains. Severe endemic selenium deficiency is found in humans in the long mountainous belt extending from south-central to northeast China; a relatively low selenium status is found in New Zealand, Finland (before the use of selenium fertilizers), and southern and eastern China. In contrast, seleniferous conditions are found in northern Nebraska and the Dakotas, and clear selenosis has been identified in humans in three counties in central China and in parts of Colombia and Venezuela. The geographic variation in the selenium status of food chains concerns both the amounts and chemical forms of selenium distributed in the world's soils. Elemental selenium and its reduced inorganic forms (selenides) are insoluble in aqueous solvents; selenites can form stable adsorption complexes with ferric hydroxide. These forms tend not to be leached (selenates) and many organic forms (selenium analogues of methionine or cysteine) are soluble in water and tend to be well used by both plants and animals. Accordingly, the moisture level, pH, aeration, and redox conditions of soils can affect the availability to plants of the selenium contained therein. In soils that are slightly acid to neutral, selenium is present largely in organic compounds formed from the vegetation growing there; harvesting crops from such soils can deplete the soils' selenium contents. Soils that are alkaline and fairly dry can support plant selenium concentrations (predominantly as selenate) great enough to be toxic to animals. Fan and Kizer refer to some seleniferous soils; they do not point out, however, that selenium availability can vary tremendously among soils from different locations and that the total soil selenium content is a poor indicator of the availability of the element to plants and, hence, to the food chain. They correctly mention that some plant species can accumulate high tissue concentrations of selenium when grown on seleniferous soils. Such "selenium-accumulator plants"—genera *Astragalus, Machaeranthera, Haplopapus, Stanleya, Aster, Atriplex,* and others—have the metabolic facility to concentrate available soil selenium to levels approaching thousands of parts per million (dry weight basis) primarily in the form of Se-methylselenocysteine. It should also be emphasized that most plant species do not concentrate such high levels of selenium. Even when grown under seleniferous conditions, nonconcentrator species rarely accumulate more than 1 to 4 parts per million selenium, and the risk of selenosis related to their consumption must be considered low. As Fan and Kizer point out, selenosis of apparent food origin has been reported in humans only in a small number of geographically distinct, isolated locales each characterized by extraordinarily great soil concentrations of highly available forms of selenium. All other documented cases of selenosis in humans have involved the misuse of selenium-rich solu-

tions—such as gun-bluing, selenium sulfide-containing shampoos—an erroneously formulated oral supplement, or industrial exposure (primarily to selenium aerosols).

Fan and Kizer mention that, in some respects, the metabolism of selenium compounds is similar to that of their S-analogues. Selenomethionine is catabolized slowly and can be incorporated directly into proteins in lieu of methionine. Although this substitution seems to have no immediate physiologic consequence, the nonspecific incorporation of selenium into proteins by this route competes with the specific incorporation of the element into physiologically important selenium-dependent proteins. In contrast, selenocysteine appears to be catabolized rapidly to release its selenium moiety in a form (apparently a selenide) that is also produced from the oxidized inorganic selenite and selenates. The metabolic production of this common form, which appears to be a precursor to the selenocysteine found in the selenium-dependent proteins—such as glutathione peroxidase, selenoprotein "P"—means that the use of these different chemical species is similar. Thus, the nutritional activities of selenite and selenocysteine tend to be similar to and greater than that of selenomethionine. This fact is important to bear in mind, as it makes understandable the otherwise anomalous finding that two major forms of selenium in foods—selenomethionine in foods derived from plants and selenocysteine in foods derived from animals—have different metabolic fates and thus different bioavailabilities, although both may support comparable concentrations of the element in tissues.

In understanding the complexity of issues concerning the role(s) of selenium in health, it will be helpful to keep in mind a few key points. First, it is clear that selenium is an essential nutrient and that its function in the enzyme glutathione peroxidase has fundamental importance probably to all cells and, thus, to all organs in protecting against oxidative stress. This function may relate to recent findings suggestive of a protective role of selenium in cancer and cardiovascular diseases. Second, present information indicates that most American adults consume more than 55 or 70 μg selenium per day, the levels recently set as the recommended dietary allowances—for women and men, respectively.[5] In a few cases involving the use of refined liquid feeding solutions that are known to be low in selenium (total parenteral nutrition solutions), the use of selenium supplements is recommended; for healthy persons consuming mixed diets, however, selenium supplements are not likely to be beneficial. Third, though selenium compounds can be toxic, the likelihood of selenosis is only important in association with an excessive use of supplements: greater than about 500 μg total selenium per day for adults.

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Eicosanoids and Hypertension

WILSON AND CO-WORKERS elsewhere in this issue of the journal review evidence for the role of prostaglandins, particularly those in the kidney, as potentially causal, if not contributory, to systemic hypertension.[1] The authors hypothesize that the renal synthesis of thromboxane A_2 is the key prostanoid in this process. The notion is that an excess of the vasoconstricting properties of thromboxane relative to vasodilating properties of other prostanoids such as prostacyclin (prostaglandin I_2) results in increased renal vascular resistance, which in turn triggers systemic elevations of blood pressure.

The hypothesis is debatable. Cytochrome P-450-derived arachidonate metabolites may be mediators of systemic hypertension. Groups at New York Medical College (Valhalla, NY) and Vanderbilt University (Nashville, Tenn) have demonstrated the kidney's capacity to synthesize a variety of cytochrome P-450 arachidonate metabolites and have shown that these compounds have both hemodynamic and tubular effects.[2-4] Of interest is an observation that inhibiting the renal synthesis of these products in spontaneously hypertensive rats blocks the development of hypertension in this genetic model.[5] It is possible that the evidence implicating renal thromboxane—which is the genesis of the hypothesis of Wilson and associates—represents an epiphenomenon and that a different aspect of the arachidonate cascade is implicated. On the other hand, contributions may occur through both pathways or, at the extreme, there may be no role of renal or systemic eicosanoids in causing hypertension.

Wilson and colleagues cite data concerning the influence of inhibitors of thromboxane synthesis and the attendant effects on renal vascular resistance. Thromboxane synthesis inhibitors are relatively poor probes of the role of thromboxane because the blockade of thromboxane formation simply results in an accumulation of the precursor endoperoxide, which can also serve as an agonist for thromboxane receptors.[6,7] Though this endoperoxide is not as effective an agonist at vascular receptors in causing vasoconstriction as it is toward platelets in causing aggregation, it seems that a thromboxane synthesis inhibitor in itself would be unable to completely ameliorate the effects of thromboxane on vascular resistance, whether systemically or in the kidney.[7] Many investigators feel that better potential probes of thromboxane pathways (and likely better therapeutic agents) will be antagonists of thromboxane receptors.[6] A number of such antagonists have been synthesized and are undergoing trials. Their use as pharmacologic tools to address hypotheses such as that put forward by Wilson and co-workers will be of great interest.

The use of a thromboxane receptor antagonist will not be sufficient to test the hypothesis of Wilson and colleagues. If a thromboxane receptor antagonist ameliorated fixed hypertension or its development, little information would be gained as to whether this was a systemic or a renal